Oral **I**ron **R**epletion effects**ON** **O**xygen **U**p**T**ake in **H**eart **F**ailure: **IRONOUT-HF**

Cardiopulmonary Exercise Testing Manual of Operating Procedures

Massachusetts GeneralHospital Cardiopulmonary Exercise Laboratory

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2. SITE ASSESSMENT AND CERTIFICATON

2.1 INTRODUCTION

The IRONOUT-HF Trial will utilize cardiopulmonary exercise testing (CPET) to derive peak VO_2 at baseline and after 16 weeks of treatment with oral iron repletion or placebo. Change in peak VO_2 will be the primary endpoint. CPET will also permit measurement of clinically relevant secondary endpoints such as workload achieved, anaerobic threshold and other indicators of cardiovascular reserve capacity.

Previousmulticenter trials evaluating exercise gas exchange have been confounded by methodological differences in exercise protocols and lack of uniformity in interpretation of gas exchange data.[1-3]The Heart Failure NetworkCPET Core Laboratory at Massachusetts General Hospital will work with individual centers to promote uniformity in CPET administration, reporting, and quality control measures. The CPET Core Laboratory recognizes that most participating laboratories have significant experience and expertise in administering CPETs. However, site assessment, certification, and strict adherence to this detailed protocol will be essential to ensure the consistency and validity of derived results. This manual has been divided into 8 sections, which include printable forms to guide sites through qualification procedures, patient education, and CPET administration.

2.2 CPET EQUIPMENT REQUIREMENTS

Cycle/Treadmill: Cycle ergometry will be the preferred exercise modality for IRONOUT-HF Trial. For CPET laboratories that do not perform cycle ergometry an alternative treadmill exercise protocol has been devised (Section 3). Regardless of the exercise modality, the metabolic cart computer should be able to control the work rate of the cycle or treadmill. Electrically-braked cycles will be required, as opposed to friction-braked cycles, based on their higher precision of work rate relative to friction-braked cycles and the ability to implement a continuous ramp protocol.[4] It will be essential to conduct the qualifying CPETs on the same equipment that will be used for the CPETs conducted for this trial.

Airflow or volume transducers: The accurate measurement of ventilation parameters during exercise is critically dependent on the accuracy of the flow-sensing device. Transducers used in exercise testing should meet established standards by the American Thoracic Society for flow and volume measurement during spirometry.[6]

Gas analyzers: Breath-by-breath analysis requires precise knowledge of gas analyzer delays and response kinetics.[7] Participating laboratories will need to follow standards for gas analyzer performance in breath-by-breath mode; these will include a transfer delay time of <1 second, a rise time <0.1 seconds, calibration stability of ± 3% over 20 min and calibration linearity ± 3% over the entire range.[8] Each site will be required to maintain a calibration logbook so that long-term trends can be monitored.

Electrocardiographic monitoring: Participating laboratories will be required to use electrodes and detection electronics designed for movement artifact rejection. Silver or silver chloride electrocardiogram (ECG) electrodes with circumferential adhesive provide good electrical

contact and minimize movement artifact. Continuous display of ECG tracings with 12-lead ECG placement as described by Mason and Likar.[10] The timing of ECG monitoring must be synchronized with the timing used by the gas exchange system, preferably through an integrated ECG-metabolic cart system. ECGs will be performed for precise heart rate monitoring and for safety purposes, but will not be transmitted to the core lab for interpretation.

Metabolic measurement systems: The core laboratory encourages sites to utilize standard metabolic cart processing software.This will promote uniform generation, formatting and acquisition of breath-by-breath data. Medgraphics Inc (St. Paul, MN) metabolic carts interfaced with BREEZESUITE software represent the most commonly used metabolic measurement systems in the United States and the primary equipment used by the Core Laboratory. Therefore CPET data acquired and configured with BREEZESUITE software is preferred. The second most common type of metabolic cart used in CPET is Viasys (previously Sensormedics), which the core lab is equipped to interpret. For Viasys/Sensormedics equipment, sites will be strongly encouraged to use ENCORE/Vmax software formatted data to facilitate data manipulation and simple transfer of data to the core laboratory. If an alternative metabolic measurement system is utilized (i.e. Parvomedics), it must allow real-time tabular and graphical display of exercise variables, 5-of-7 breath moving average integration of gas exchange variables, and data conversion to unencrypted format such as Excel that will lend itself to interpretation by the core laboratory.

2.3 CPET EQUIPMENT CALIBRATION

CPET equipment should be calibrated by following instructions given by the manufacturer of the equipment, and in accordance with the schedule outlined below. Participating sites will be required to maintain a calibration logbook.

Prior to performance of CPETs for IRONOUT-HF,the following calibration procedures are recommended but not required.

1. Electrically braked cycle ergometers that have not been previously calibrated or newly purchased should be dynamically calibrated with the use of a dynamometer (torque meter). Because many labs do no have dynamometers, cycle ergometer manufacturers may be required to provide this service. This calibration should be repeated if the cycle is moved or jarred or if certification testing results in abnormal values for gas exchange-work rate relationships.
2. Treadmills should have belt speed verified by timing revolutions using a mark made on the treadmill belt with a subject on the treadmill. Grade may be determined by using a plumb line and tape measure.

Every 12 months

1. Physiologic calibration: A healthy volunteer, consuming a stable diet performs a constant work rate test (i.e. 50 W and 100 W) in which steady state values for V_E, VCO_2, VO_2 are compared to those of previous tests. Coefficients of variation (%CV) should be below 5% for repeat oxygen uptake measurements and below 7% between repeat sessions, with values outside of the 95% confidence interval engendering system-wide reassessment.

Prior to each test

1. Record barometric pressure, temperature, relative humidity
2. Perform flow calibration with a 3L syringe (<1-15sec duration) to achieve ± 3% agreement with calculated volumes.
3. Perform gas analyzer calibration with two precision-analyzed gas mixtures. This is commonly done with one 6% CO_2 and 15% O_2 tank and one 0% CO_2 and 21% O_2 tank. The air baseline setting for O_2 and CO_2 should be checked before each test to correct for baseline drift since calibration.
4. Determine transport delays between the gas sampling point and each gas analyzer. This should be an automated process.

2.4 SITE QUALIFICATION PROCEDURES

Before baseline studies may be performed in subjects, each site will be required to submit two incremental symptom-limited CPET tests on a "standard normal subject". The standard subject should be a healthy adult. Sites have often used laboratory employees for qualification testing. These tests must be performed on separate days, preferably no more than 5 days apart, according to the protocol summarized in Section 7. Prospective CPET laboratories will be evaluated based on their ability to: (1) follow a site qualification protocol (see Figure 2 and Tables 7 and 8), (2) generate reproducible CPET data, and (3) transmit data to the core laboratory. Test results will be compared to data available on normal individuals from the core laboratory and the published literature.[8, 11] Sites should await feedback from the core laboratory confirming that their site has qualified prior to scheduling study patients for testing.

Sites may subsequently use repeated studies of the "standard normal subject" to verify accuracy of their systems. The Core Laboratory will require sites to maintain a detailed log of physiologic calibration testing as described above, but this information will not need to be transmitted to the core laboratory as part of the initial qualifying procedures.

In anticipation of transmitting qualification tests to the core laboratory the individual who will be transmitting data from the participating CPET laboratory to the core laboratory should take the following steps (also see Appendix 1): Email Diane Cocca-Spofford RN at dcoccaspofford@partners.organd CC glewis@partners.organd indicate the following:

   a. Regional research site name.
   b. Responsible CPET lab staff member who will primarily interact with the Core Laboratory with email address and contact information.
   c. Exercise modality that will be used for the clinical trials (cycle or treadmill)
   d. Metabolic cart manufacturer and software program that will be used.
2. Await receipt of an email from Diane Cocca-Spofford with an invitation to join Partners Research Computing network through which qualification study files and subsequent study files can be transferred via email (see Section 4 for detailed instructions).
3. Transmit the two qualification studies formatted as described below and summarized in Tables 7 and 8.

3.CPET PROCEDURES

3.1 CPET Preparation

The protocol for symptom-limited CPET testing forIRONOUT is displayed schematically in Figures 2 and 3. Cycle ergometry will be the preferred exercise modality with a ramped workload of10 watts/min For CPET laboratories that do not perform cycle ergometry an alternative treadmill exercise protocol has been devised that simulates cycle ergometry in terms of a linear, comparable increment in external work performed and a gradual increment in both speed and ramp that is appropriately suited to the study of HF patients.[12] In order to achieve within subject consistency, it is important that a laboratory that elects to perform treadmill ergometry commit to doing so for all study tests that it performs. In addition, if a participating laboratory has more than one ergometer or metabolic cart, the same equipment should be used for each test in a given subject.

1. **Patients should be given pre-test instructions according to your institution's CPET laboratory practice.** The Patient Education Form, Section 6 is provided as an example instruction sheet that can be used at the discretion of participating laboratories. Subjects should be given instructions to follow the same regimen of fasting (for at least 3 hours) and taking their medications prior to testing, particularly medications that influence heart rate.

2. **Review of contraindications to exercise testing**. Table 1 lists contraindications to exercise testing which are anticipated to be very rare within patients enrolled in IRONOUT-HF. Questions that arise regarding exercise eligibility should be brought to the attention of the site principal investigator.

Table 1: Contraindications to Exercise Testing:

Absolute Contraindications
• Acute myocardial infarction (3-5 days) or unstable angina • Uncontrolled symptomatic arrhythmias • Active endocarditis • Acute myocarditis or pericarditis • Symptomatic severe aortic stenosis • Acute pulmonary embolism or DVT • Suspected dissecting aneurysm • Uncontrolled asthma • Uncontrolled pulmonary edema • Room air desaturation to <85% • Acute non-cardiopulmonary disorder that may affect exercise performance (infection, orthopedic problem) • Mental impairment leading to inability to cooperate • History of exercise-induced ventricular arrhythmia

3. **Spirometric evaluation** should be completed upon arrival to the CPET laboratory by all sites that routinely include this test as part of the standard CPET procedure. This will

7.3 IRONOUTHF 10 Watt Ramp CYCLE ERGOMETER PROTOCOL

Table 9. CPET exercise worksheet for subjects performing 10W/min ramp cycle ergometry

HCM♥NET CPET CORE PROTOCOL SYNOPSIS AND SUPPLMENTAL DATA SHEET

Referring Center Name and Number:		**Hemoglobin**	
Subject/Test NAME:		**Time of study med**	
Date and time at start of exercise:		**Seat height (cm)**	
Technician of record:		**FEV1**	
Reason for cessation of exercise		**FVC**	

Elapsed Time(min)	Work Rate Increase 10 W/min	Target Pedal Rate (rpm)	Actual Pedal Rate (rpm)	HR (bpm)	O_2 sat (%)	SBP (mmHg)	DBP (mmHg)	Borg Dyspnea (1-10)
-1 (Pre)	Rest	0						
0-5	Rest	0						
5-8	0	60						
8-9	10	60						
9-10	20	60						
10-11	30	60						
11-12	40	60						
12-13	50	60						
13-14	60	60						
14-15	70	60						
15-16	80	60						
16-17	90	60						
17-18	100	60						
18-19	110	60						
19-20	120	60						
20-21	130	60						
21-22	140	60						
22-23	150	60						
23-24	160	60						
24-25	170	60						
>25	10/min	60						
Time:	**W:**							
Rec. 1 min	5	30						
Rec. 2 min	rest	0						
Rec. 3 min	rest	0						
Rec. 4 min	rest	0						
Rec. 5 min	rest	0						
Rec. 6 min	rest	0						
Rec. 7 min	rest	0						
Rec. 8 min	rest	0						
Rec. 9 min	rest	0						
Rec. 10 min	rest	0						

*Recordings should be made during the last 15 sec of each minute

7.4 IRONOUT: TREADMILL PROTOCOL. Designed to mirror cycle ergometry protocol with a ≈10W/min incremental protocol

Table 10. CPET exercise worksheet for subjects performing 10W/min treadmill ergometry assuming subject weight <= 80 kg

HCM♥NET CPET CORE TREADMILL PROTOCOL SYNOPSIS AND SUPPLMENTAL DATA SHEET					
Referring Center Name and Number:			**Hemoglobin**		
Subject/Test NAME:			**Time of study med**		
Date and time at start of exercise:					
Technician of record:			**FEV1**		
Reason for cessation of exercise			**FVC**		

Elapsed Time (min)	Work Rate (W)	Speed (mph)	Grade (%)	HR (bpm)	O_2 sat (%)	SBP (mmHg)	DBP (mmHg)	Borg Dyspnea (1-10)
-1 (Pre)								
0-5	Rest	Rest	0					
5-8	5	0.8	2					
8-9	15	1	5					
9-10	24	1.1	7					
10-11	33	1.3	8.5					
11-12	43	1.5	9.5					
12-13	51	1.6	10.5					
13-14	60	1.8	11					
14-15	70	2	11.5					
15-16	80	2.2	12					
16-17	88	2.3	12.5					
17-18	100	2.5	13					
18-19	111	2.7	13.5					
19-20	123	2.9	14					
20-21	137	3.1	14.5					
21-22	150	3.3	15					
22-23	165	3.5	15.5					
23-24	180	3.7	16					
24-25	195	3.9	16.5					
>25		+0.2/min	+0.5/min					
Peak: t_____								
Rec. 1 min	5	1.0	0					
Rec.2 min	0	rest	0					
Rec. 3 min	0	rest	0					
Rec. 4 min	0	rest	0					
Rec. 5 min	0	rest	0					

Rec. indicates recovery, W indicates watts, HR indicates heart rate, SBP indicates systolic blood pressure, DBP indicates diastolic blood pressure, t indicates time of cessation of exercise.

Table 10b. CPET exercise worksheet for subjects performing treadmill ergometry
Designed to mirror cycle ergometry protocol with a ≈10W/min incremental protocol assuming subject weight > 80 kg

HCM♥NET CPET CORE TREADMILL PROTOCOL SYNOPSIS AND SUPPLMENTAL DATA SHEET					
Referring Center Name and Number:			**Hemoglobin**		
Subject/Test NAME:			**Time of study med**		
Date and time at start of exercise:					
Technician of record:			**FEV1**		
Reason for cessation of exercise			**FVC**		

Elapsed Time (min)	Work Rate (W)	Speed (mph)	Grade (%)	HR (bpm)	O_2 sat (%)	SBP (mmHg)	DBP (mmHg)	Borg Dyspnea (1-10)
-1 (Pre)	0	Rest	0					
0-5	0	Rest	0					
5-8	5	0.8	1.5					
8-9	16	1	4					
9-10	24	1.1	5.5					
10-11	36	1.3	7					
11-12	44	1.5	7.5					
12-13	50	1.6	8					
13-14	60	1.8	8.5					
14-15	70	2	9					
15-16	82	2.2	9.5					
16-17	90	2.3	10					
17-18	98	2.5	10					
18-19	111	2.7	10.5					
19-20	125	2.9	11					
20-21	140	3.1	11.5					
21-22	155	3.3	12					
22-23	164	3.5	12					
23-24	181	3.7	12.5					
24-25	191	3.9	12.5					
>25		+0.2/min	+0.5/min					
Peak: t____								
Rec. 1 min	5	1	0					
Rec.2 min	0	rest	0					
Rec. 3 min	0	rest	0					
Rec. 4 min	0	rest	0					
Rec. 5 min	0	rest	0					

Rec. indicates recovery, W indicates watts, SBP indicates systolic blood pressure, DBP indicates diastolic blood pressure, t indicates time elapsed upon cessation of exercise.

8. IRONOUT-HF CPET CORE LAB PERSONNEL

Primary Contact:

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APPENDIX 1: Form 001 IRONOUT-HF CPET Core Lab

Site Qualification Procedures Checklist:

☐ Verify your site's compliance with equipment requirements and calibration procedures.

☐ Email Diane Cocca-Spofford RN at dcoccaspofford@partners.org and CC glewis@partners.organd indicate the following:

a. Responsible CPET lab staff member who will primarily interact with the Core Laboratory with email address and contact information.
b. Exercise modality that will be used for the clinical trials (cycle or treadmill)
c. Metabolic cart manufacturer and software program that will be used.

☐ Accept emailed invitation from Diane Cocca-Spofford to join the Partners Research Computing Secure Files Transfer Service (see Section 4 for detailed instructions).

☐ Submit two incremental symptom-limited CPET qualifying tests on a "standard normal subject" (see Section 7, protocol specific worksheets) via the Partners Computing Secure Files Transfer Service.

CPET Procedures Checklist:

☐ Print and distribute patient education forms (Section 6) to subjects at least 48 hours prior to testing and assess compliance with instructions upon the subject's arrival to the laboratory.

☐ Obtain the subject's study ID number from your site's research coordinator.

☐ Assess CPET contraindications (Table 1).

☐ Print Borg Score Table for use during CPET (section 6).

☐ Perform spirometry and record results in metabolic cart software program.(optional)

☐ Configure gas exchange data output according to Table 5.

☐ Enter current hemoglobin level and cycle seat height into CPET electronic file.

☐ Complete CPET according to the appropriate protocol (sections 3 and 7), integrate all study data into a single CPET file, and name the file according to section 4.1.

☐ Save a backup copy of the CPET file on a disk that will be maintained in individual CPET laboratories and transmit the electronic file to the core laboratory.

☐ Transmit data file to the core laboratory.

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